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COZEN O'CONNOR, P.C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508

EXAMINER	
SANG, HONG	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/731,759
Filing Date: December 08, 2003
Appellant(s): KING ET AL.

Doreen Yatko Trujillo
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11/23/2009 appealing from the Office action mailed 12/26/2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,670,132	Griffiths et al.	9-1997

Zapata et al. "Site-specific Coupling of Monomethoxypoly(ethylene glycol) to a Single Sulfhydryl humanized Fab'", FASEB J., 1995, 9:A1479.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zapata et al. (FASEB J. 1995. 9:A1479; IDS-12/13/2004) in view of Griffiths et al. (U.S.

Patent 5,670,132, Pub. Date: 9/23/1997, earliest effective filing date: 09/20/1994; IDS – 12/13/2004).

Zapata et al. teach a Fab' fragment which contains a single free thiol in the hinge region including the coupling of monomethoxypoly(ethylene glycol) (MePEG) to the thiol, wherein the MePEG is 5 kDa or 10 kDa (see abstract). Zapata et al. disclose that both 5 kDa and 10 kDa MePEG-Fab' species have reduced clearance compared to the native Fab' molecule, with that of the 10 kDa form reduced further than the 5 kDa form (see the abstract). Zapata et al. disclose that modification of the Fab' fragment with either size of MePEG maleimide did not affect the ability of this molecule to bind to its antigen. Zapata et al. teach that the ability to modify the clearance rate of an antibody Fab' fragment by attaching a single MePEG moiety at a unique site, without affecting antigen binding, increases significantly the potential therapeutic value of the this type of molecule. A Fab' fragment containing a single free thiol in the hinge region meets the claims limitation: a monovalent antibody fragments comprising a heavy chain and light chain, wherein the heavy chain consisting of VH-CH1, the light chain consisting of VL-CL, a hinge domain contains only one cysteine residue (one cysteine residue contains only one thiol group). The polymer is attached to the single sulfhydryl group in the hinge region.

Zapata et al. do not teach the polymer of 25,000 Da to about 40,000 Da, an antibody fragment covalently attached to one or more effector or reporter molecules, and a pharmaceutical composition with a carrier. However, these deficiencies are made up for in the teachings of Griffiths et al.

Griffiths et al. disclose that it is known that PEG conjugation to proteins can prolong serum half-life of proteins, and PEG conjugation to Fab' antibody fragment can dramatically reduce renal uptake and retention of Fab' antibody fragments (see column 2, lines 46-48). Griffiths et al disclose site specific conjugation of PEG to antibody fragments including Fab' outside the variable region (see column 3 and 4), including a thiol group in the hinge region of the antibody fragment (see column 3, line 24). Griffiths et al. teach that PEG preparations with a wide variety of average molecular weight can be prepared and used for this invention (see column 3, lines 12-13), for example PEGs having average molecular weight of the PEG can be 1,000-30,000 Da (column 3, lines 12-19), which overlaps with the claimed range 25,000 Da-40,000 Da. Griffiths et al further teach an antibody conjugated to 1-10 PEG-5,000 moieties to reduce renal uptake and retention of the PEGylated antibody fragment after radiolabeling (claim 15 and 16, in particular), indicating a wide variety of average molecular weight can be used for PEGylation of an antibody. In addition, Griffiths et al. teach an PEGylated antibody fragment having an detector label attached (see abstract) including compositions comprising such antigen binding fragments and a pharmaceutically acceptable carrier (column 6, lines 62-67 in particular).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a Fab' fragment covalently linked to a polymer molecule having an average molecular weight higher than 10,000 Da such as 20,000-30,000Da, and further covalently attached to an effector or reporter molecule, and pharmaceutical compositions comprising such antibody fragments in

view of Zapata and Griffiths. One would have been motivated to have used MePEG with molecular weight higher than 10,000 Da such as 20,000-30,000 Da MePEG because Zapata et al. have shown that MePEG with higher molecular weight (10 kDa) reduced further clearance of Fab' antibody fragment compared to MePEG with lower molecular weight (5 kDa), and Griffiths et al. teach that a wide variety of average molecular weight can be used for PEGylation of an antibody, including 5,000-30,000 Da. One would have been motivated to have made a pharmaceutical composition comprising such an antibody fragment, and/or attached an effector or reporter molecule to said antibody fragment because Zapata et al. teach that the ability to modify the clearance rate of an antibody Fab' fragment by attaching a single MePEG moiety at a unique site, without affecting antigen binding, increases significantly the potential therapeutic value of the this type of molecule, and Griffiths teach that PEG modified radiolabeled antibody fragments are useful for radioimmunodetection of tumors and infectious lesions and display striking reductions in renal uptake and retention of radioisotope compared to non-PEG modified fragments (see abstract). One would have a reasonable expectation of success to have produced a Fab' fragment covalently linked to a polymer molecule having an average molecular weight higher than 10,000 Da such as 20,000-30,000Da, and further covalently attached to an effector or reporter molecule, and pharmaceutical compositions comprising such antibody fragments because methods of making PEG modified Fab' and radiolabeled Fab' fragments were well known in the art as shown by Zapata and Griffiths.

(10) Response to Argument

The Brief states that Griffiths does not disclose a PEG having a molecular weight of 30,000 Da. Instead, Griffiths discloses a range of suitable molecular weight of 1,000-30,000 Da for PEGS (see the Brief, page 4, last paragraph). In addition, Griffiths discloses the use of 1-10 5,000 Da PEGS, not the attachment of one PEG of a molecular weight ranging from 5,000-50,000 Da (see the Brief, page 5, last paragraph). The Brief states that Griffiths does not teach a hinge domain which contains only one cysteine residue (see page 5, last paragraph). The Brief states that Griffiths teaches attaching radiolabels to the hinge regions cysteines, not a polymer, as such Griffiths teaches away from the claimed invention (see the Brief, page 6, paragraph 3).

Appellant's arguments have been carefully considered but are not persuasive. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Zapata et al teach a Fab' fragment which contains a single free thiol in the hinge region including the coupling of monomethoxypoly(ethylene glycol) (MePEG) to the thiol, wherein the MePEG is 5 kDa or 10 kDa (see abstract). Because the primary reference (Zapata et al.) explicitly teaches coupling a polymer to the single thiol in the hinge region of a Fab' fragment, the arguments that the secondary reference (Griffiths) does not teach such limitation and teaching away are not persuasive. Contrary to Appellant's assertion, Griffiths et al. also disclose site specific conjugation of PEG to antibody fragments including Fab' outside the variable region (see column 3 and 4),

including a thiol group in the hinge region of the antibody (see column 3, line 24). The secondary reference Griffiths was cited by examiner to show that PEG with a wide variety of average molecular weight can be linked to an antibody. Griffiths et al. teach that PEG preparations with a wide variety of average molecular weight can be prepared and used for this invention (see column 3, lines 12-13), for example PEGs having average molecular weight of the PEG can be 1,000-30,000 Da (column 3, lines 12-19), which overlaps with the claimed range 25,000 Da-40,000 Da. MPEP §2144.05 states that in the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).* Given the teachings of Zapata that MePEG with higher molecular weight (10 kDa) reduced further clearance of a Fab' antibody fragment compared to MePEG with lower molecular weight (5 kDa), and Griffiths that a wide variety of average molecular weight including 1,000-30,000 Da can be used for PEGylation of an antibody fragment, one skilled in the art would have been motivated to have used MePEG with higher molecular weight such as 20,000-30,000 Da taught by Griffiths for purpose of further reducing clearance of the Fab' fragment. With respect to the arguments of teaching away from the invention of claim 15, although Griffiths et al. teach that the radioisotope is preferably linked to the thiol group in the hinge region, they also teach that the radioisotope can be linked to an introduced thiol group. Griffiths et al. teach thiolating the antibody fragment by introduction of ligands containing thiol groups by conventional procedures, either non-site specifically or on a carbohydrate moiety, preferably one

which has been engineered onto a light chain constant region of the fragment (see column 5, lines 10-15). Given the teachings of Griffiths that that a radioisotope can be coupled to PEG antibody fragments at more than one site, one skilled in the art would conclude that Griffiths et al. do not teach away from the invention of claim 15. Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971).*

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Hong Sang/

Examiner, Art Unit 1643

Conferees:

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643

Gary Nickol

/Gary B. Nickol /

Supervisory Patent Examiner, Art Unit 1646